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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,891	03/31/2006	Tatsuo Hoshino	21421 US C038435/0185661	4642

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,891	HOSHINO ET AL.	
	Examiner	Art Unit	
	CHRISTIAN L. FRONDA	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3, and 6-8 in the claim set filed 10/10/2008 are pending and under consideration in this Office Action. New grounds of rejection are presented in the instant Office Action.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3, and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The recitation of "a synergistic enzyme combination" in amended claim 1 represents a departure from the specification and the claims as originally filed. The "synergistic enzyme combination" as recited in amended claim 1 was not originally disclosed in the specification and the claims as filed. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 U.S.C. § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

According to MPEP 2143:

> "Exemplary rationales that may support a conclusion of obviousness include:
>
> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) " Obvious to try " – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.
>
> Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel."

5. Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J Bacteriol. 1995 May;177(10):2804-12; REFERENCE OF RECORD) in view of the combined teachings of Sprenger et al. (Proc Natl Acad Sci U S A. 1997 Nov 25;94(24):12857-62; REFERENCE OF RECORD) and Laber et al. (FEBS Lett. 1999 Apr 16;449(1):45-8; REFERENCE OF RECORD). The arguments filed 10/10/2008 have been fully considered but are not persuasive for the reasons of record as supplemented below.

Zhao et al. teach a recombinant *Escherichia coli* capable of producing vitamin B6 comprising extra nucleic acids from *Escherichia coli* (*epd* gene) encoding erythrose 4-phosphate dehydrogenase, which is expected to be amplified using the recited PCR primers of SEQ ID NOs: 1 and 2. See entire publication, especially pages 2804-2810, Figs. 1 and 2, and Tables 1-3.

The teachings of Zhou et al. differ from the claims in that the recombinant *Escherichia coli* does not carry extra nucleic acids encoding 1-deoxy-D-xylulose 5-phosphate synthase and pyridoxol 5'-phosphate synthase.

Sprenger et al. teach the nucleic acid from *Escherichia coli* encoding 1-deoxy-D-xylulose 5-phosphate synthase, which is required for the formation of the 1-deoxy-D-xylulose 5-phosphate precursor to vitamin B6 and is expected to be amplified using the recited PCR primers of SEQ ID NOs: 5 and 6. See entire publication, especially pages 12857-12861 and Figs. 1-4.

Laber et al. teach the nucleic acid from *Escherichia coli* encoding pyridoxol 5'-phosphate synthase (PdxJ protein), which in combination with 4-(phosphohydroxy-L-threonine dehydrogenase (PdxA protein) catalyzes the formation of vitamin B6 and is expected to be amplified using the recited PCR primers of SEQ ID NOs: 9 and 10. See entire publication, especially pages 45-47.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the recombinant *Escherichia coli* of Zhao et al. such that the *E. coli* nucleic acid encoding 1-deoxy-D-xylulose 5-phosphate synthase taught by Sprenger et al. and the *E. coli* nucleic acid encoding pyridoxol 5'-phosphate synthase taught by Laber et al. are transformed and overexpressed in the recombinant *Escherichia coli* of Zhao et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have the advantage of a recombinant *Escherichia coli* that can overproduce Vitamin B6 due to the overexpressed and overproduced enzymes within the modified recombinant *Escherichia coli* of Zhao et al. Because Sprenger et al. teach 1-deoxy-D-xylulose 5-phosphate synthase is required for the formation of the 1-deoxy-D-xylulose 5-phosphate precursor to vitamin B6 and Laber et al. teach pyridoxol 5'-phosphate synthase (PdxJ protein) which in combination with 4-(phosphohydroxy-L-threonine dehydrogenase (PdxA protein) catalyzes the formation of vitamin B6, then the modified recombinant *Escherichia coli* of Zhao et al. with overexpressed and overproduced vitamin B6 synthesizing enzymes would inherently have a synergistic enzyme combination that that can overproduce Vitamin B6. One of ordinary skill in

the art at the time the invention was made would have a reasonable expectation of success because the art of molecular biology and recombinant manipulations of *E. coli* host cells are well known and developed.

According to MPEP 2145, argument does not replace evidence where evidence is necessary. It is noted that applicants have not provided an appropriate affidavit or declaration containing factual evidence that refutes, contradicts, and discredits the teachings and operability of the combination of the references. In response to the arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). According to MPEP 2144, it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicants. Although teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention is an appropriate method for determining obviousness; however, it is just one of a number of valid rationales for doing so. The Supreme Court in *KSR* identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper functional approach to the determination of obviousness as laid down in *Graham*, which is stated above in MPEP 2143. The obviousness rejection stated above for the amended claims relied on combining prior art elements according to know methods to yield a predictable result in which the result is the advantage of a recombinant *Escherichia coli* that inherently has a synergistic enzyme combination that that can overproduce Vitamin B6.

6. Claims 3 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. in view of the combined teachings of Sprenger et al. and Laber et al. as applied to claim 1 above, and further in view of Yang et al. (J Bacteriol. 1998 Aug;180(16):4294-9; REFERENCE OF RECORD). The arguments filed 10/10/2008 have been fully considered but are not persuasive for the reasons of record and for the reason stated above for the rejection of amended claim 1.

Yang et al. teach a process for preparing vitamin B6 comprising culturing recombinant *Escherichia coli* strains having the *epd* gene encoding erythrose 4-phosphate dehydrogenase in LB medium (fermentation broth) containing 1% glycerol and 1% succinate at 37°C for about 24 hours. Yang et al. further teach HPLC chromatography to identify B6 vitamers. See entire publication especially pages 4294-4298, Figs. 1-3, and Tables 1-3.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Yang et al. such that the modified recombinant *Escherichia coli* of Zhao et al., which inherently has a synergistic enzyme combination that that can overproduce Vitamin B6, is used in the process for preparing vitamin B6 taught by Yang et al. and the produced vitamin B6 separated from the fermentation broth. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a fermentation method that will allow production of large amounts of vitamin B6. Furthermore, it is within the preview of one of ordinary skill in the art at the time the invention was made to use and optimize the recited temperature, pH, nutrients, carbon source, nitrogen source, inorganic salts, and culturing conditions in order to facilitate optimal production of vitamin B6.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571)272-0934. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

9. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian L. Fronda/
Primary Examiner
Art Unit 1652